NTP Research Concept: Naturally Occurring Asbestos and Related Mineral Fibers

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Nomination Rationale and Background

Naturally occurring asbestos and related mineral fibers were nominated in 2006 by the National Center for Environmental Health/Agency for Toxic Substances and Disease Registry and the U.S. Environmental Protection Agency (http://ntp.niehs.nih.gov/go/29287). These nominations were based on widespread community exposure in certain geographic locales and insufficient dose-response information to characterize risk from exposure to non-commercial and "unregulated" asbestiform mineral fibers. The preliminary study recommendations for these nominations are for mineral characterization, *in vitro* durability and toxicity studies, and subchronic and chronic toxicity/carcinogenicity studies via inhalation. Studies should utilize test materials representative of minerals identified in Libby, MT and at other Naturally Occurring Asbestos (NOA) sites. Both agencies expressly requested studies that will inform whether there are toxicological differences in mineral particles that are considered asbestiform and those that are not asbestiform but are of similar chemical composition (mineralogy) and dimension (morphology). The U.S. EPA nomination mentions several specific minerals of interest, including Libby amphibole, edenite, ferroactinolite, anthophyllite, tremolite, winchite, richterite, and erionite (U.S. EPA, 2006).

Asbestos is a generic commercial term describing several silicate minerals where crystalline growth produces very long, thin, flexible, separable fibers. The six asbestos minerals recognized by regulatory authorities are the fibrous serpentine mineral, chrysotile, the amphibole minerals crocidolite and amosite, and the asbestiform varieties of the amphibole minerals tremolite, actinolite, and anthophyllite. Non-asbestiform varieties of amphibole minerals consist of crystalline particles of various shapes and sizes, some of which may be "fiber-like". The term cleavage fragment is used for elongated particles that break off from massive forms of non-asbestiform amphibole minerals along specific crystallographic planes, usually as the result of mechanical processes, e.g. during commercial processing. Asbestos occurs naturally in many parts of the United States (ATSDR, 2007), and community exposure to asbestos fibers can increase in areas where the earth is disturbed through mining, building, or other activities. These minerals rarely occur in nature as homogenous mineral deposits and exist as a continuum of particles of varying sizes, shapes, and chemical composition. Two geographical areas of current public health scrutiny, Libby, MT and El Dorado County, CA, highlight some of the issues faced and the gaps in knowledge. Libby is the site of a former vermiculite mine. Vermiculite is not asbestos or fibrous; however, the Libby vermiculite contained substantial amounts of asbestiform and non-asbestiform fibrous amphiboles (winchite, richterite), and minor amounts of asbestiform tremolite, prismatic and acicular tremolite crystals and amphibole cleavage fragments. The incidence of asbestosis, lung cancer, and mesothelioma in this community is higher than would be expected (ATSDR, 2003a). However, the relative contribution of these different mineral exposures to disease cannot be ascertained from the human studies. In El Dorado, NOA exposures have been documented at a local school and community recreation areas (U.S. EPA, 2005); however, the health implications of these findings have been challenged based on arguments that the observed fibers are not asbestos but cleavage fragments and are of low to no health risk.

Asbestos exposure is associated with a spectrum of pulmonary and thoracic disease including lung cancer, mesothelioma, asbestosis, and pleural disease. Evidence for an association between asbestos exposure and certain other cancers is suggestive but considered insufficient (Institute of Medicine, 2006). Exposure to other fibrous minerals such as erionite and some synthetic vitreous fibers has also been associated with adverse pulmonary effects including lung cancer. Toxicology studies of "non-regulated" amphibole minerals such as winchite and richterite are lacking although these minerals are known to occur in the asbestiform habit. Of the available epidemiological and animal toxicological studies on asbestos, many included exposure to both asbestiform fibers and non-asbestiform particles including cleavage fragments. Because of mixed exposures and incomplete characterization of test materials in the experimental studies, it has been difficult to relate specific adverse effects to specific sizes/types of fibers. Public health and regulatory agencies have used, in some cases, inconsistent approaches to identifying and analyzing mineral fibers and do not make clear distinctions regarding the relative hazard/risk of fibers of differing mineralogy and morphology. Most federal health agencies maintain that the best available science indicates that similarly shaped and mineralogically identical fibers should be considered a health hazard equivalent to the regulated asbestos fibers; however, agencies have been pressured to discount cleavage fragments and any fibers besides the regulated asbestos minerals. Regarding the non-asbestiform amphiboles found at NOA sites, it is important to note that much of what has been called cleavage fragments in the past are really prismatic and acicular single crystals rather than mechanically broken fragments of massive material.

Significance

Despite the known hazards of asbestiform fibers, exposures continue in certain occupations and environmental settings. The primary concern relative to this nomination is the community exposures to past and current residents of Libby, MT, former workers at the W.R. Grace vermiculite mine in Libby and vermiculite processing facilities around the country, and residents of areas where exposures to natural asbestos minerals have been documented, e.g. El Dorado Hills, CA. The primary media in which asbestos is found in these areas is soil, outdoor air, indoor dust, and indoor air. There is intense public concern regarding potential health risks from exposure to asbestos as a result of routine and recreational activities in these communities. Exposures to children are of special concern. Other stakeholders, e.g. building and building products associations, mining associations, and schools are concerned that health risks of some of the minerals might be considered as equivalent to the risks posed by commercial types of asbestos. Regulatory agencies are faced with difficult decisions in the absence of sound scientific data to assess the risk of low-level exposure to diverse types of mineral fibers.

While recognizing that asbestos in any form is an established human carcinogen, further animal studies are needed to better understand toxic and carcinogenic risk. The inherent limitations in deriving risk estimates from human studies due to incomplete exposure information leads to uncertainty in the dose-response relationship and ultimately in the potency and risk for a particular mineral fiber exposure. Evidence from human studies for cancers at sites outside the respiratory tract and non-malignant diseases such as autoimmune disorders is suggestive but these studies do not and will not in the immediate term allow definitive causal relationships to be established for these diseases. Animal studies will help elucidate the potential hazard as well as dose-response relationships for specific mineral fibers for which no health effects data exist. The U.S. EPA National Health and Environmental Effects Laboratory (NHEERL) and the National Institute for Occupational Safety and Health (NIOSH) are both developing research programs related to mineral fibers. The proposed NTP research program on mineral fibers is intended to complement these other federal research efforts. There is an established interagency asbestos working group that is serving as a forum for coordinating research among the different federal agencies. This working group will continue to provide input to the NTP in order to ensure that the proposed research program will meet public health and regulatory agency data needs. Developing collaborative research projects with academic investigators ancillary to the NTP toxicology studies is another option for increasing the scope and value of this research program.

Key Issues

The first set of issues to be addressed relate to identification, collection, and processing of suitable mineral fiber samples for toxicology studies. Site-specific mineral sample mixtures such as the Libby amphibole and El Dorado material as well as mineralogically pure samples with mixed morphology will be sought. Specific questions to be considered when designing studies include:

- Methods of processing of mineral samples to generate test materials; e.g. whether samples should be enriched for long fibers or rat respirable fibers as specified in internationally accepted fiber test guidelines.
- Value in testing non-asbestiform amphibole mineral samples containing elongated particles with fiber-like dimensions (e.g. tremolite acicular and primatic crystals, cleavage fragments).
- Whether test materials could be partially purified (size separated) without altering elemental composition, surface chemistry, or dimensional distribution.

The duration of exposure and duration of observation period (2 years or natural death, e.g. 80% mortality in any dose group) will be critical elements in testing hypotheses related to cumulative dose. Efforts to take advantage of the considerable expertise external to the NTP in asbestos and fiber toxicology will also be important in designing these studies.

Proposed Approach

The goal of this research program is to provide robust toxicological characterizations (dose-response for cancer and non-cancer endpoints) of several representative natural mineral fibers by conducting long-term inhalation studies in a rodent model. Hypotheses to be addressed include:

- Cumulative dose (as measured by lung fiber burden) is the most appropriate dose metric for predicting carcinogenic and non-carcinogenic effects of mineral fibers.
- The cumulative dose-response and relative potency differs among representative natural mineral fibers.
- Particles with similar dimensions and of similar chemical composition have equivalent toxic and carcinogenic potencies.
    - Durability (*in vitro*) and biopersistence (*in vivo*) of natural mineral fibers, a function of both mineralogy and morphology, is the primary determinant of toxic and carcinogenic potency.

- Chemical composition (mineralogy) is of secondary importance in determining toxic and carcinogenic potency.

The specific aims of the proposed research program are as follows:

Identify sources of representative natural mineral fibers. The USGS Denver Microbeam Facility, through an interagency agreement with the U.S. EPA, will be collecting material from the Libby mine ("Libby amphibole") in summer 2007. This material will be processed to closely match EPA air sampling data from the Libby area. Sufficient material will be generated for the proposed EPA/NHEERL and NTP studies. The NTP, in consultation with the USGS, ATSDR and EPA, will identify 2-3 other natural mineral fibers and sources from which to prepare suitable test materials for long-term toxicology studies. Possible sources include ferroactinolite from Minnesota, erionite from Oregon or South Dakota, and amphiboles found in El Dorado, California. Commercially available asbestos "standard" materials that have been adequately characterized previously (e.g. amosite or tremolite asbestos) will also be included as test materias for comparison to studies in the literature.

Conduct physical and chemical characterizations of test materials (mineralogy, morphology). The USGS will characterize the Libby amphibole material and advise the NTP on appropriate analytical methods for characterizing other mineral samples. Relevant characteristics include distribution of fiber length, diameter, surface chemistry, and mineral composition in a given sample by microscopic (PCM, SEM, TEM), X-ray diffraction, and electron probe microanalysis methods.

Obtain fiber durability and *in vitro* cytotoxicity data. Studies of *in vitro* dissolution of mineral fibers in simulated biological fluids or other media are used to assess fiber durability. The USGS and EPA/NHEERL have conducted or are planning to conduct dissolution and *in vitro* cytotoxicity studies for Libby amphibole and a range of commercially available asbestos standards. These data will be available for use in prioritizing and designing toxicity studies. A limited number of dissolution studies may need to be conducted for other mineral fibers being considered for study.

Conduct short-term *in vivo* assessment of biopersistence. For all selected mineral fibers, biopersistence will be assessed by evaluating lung burden following 5 or 14 day inhalation exposures and 1-90 days observation period. These studies will be used to estimate lung clearance half-life and for setting doses for subchronic studies. Short-term biopersistence of fibers has been used as an indicator of potential carcinogenic activity. Quantification of all fiber types and size in the biopersistence studies will allow for further validation of predictive carcinogenicity models evaluating relative potency of different type/size fibers.

Conduct subchronic and chronic toxicology studies. Subchronic and chronic nose-only inhalation studies will be conducted in Han-Wistar rats for Libby amphibole, a commercial asbestos material, and 1-2 other selected mineral fibers. The studies will include special assessments of pulmonary function and toxicity (bronchioalveolar lavage (BAL), cytokine measurement, markers of cytotoxicity, inflammation, and cell proliferation, and lung retention and clearance). Chronic studies will be performed with a minimum of three exposure concentrations and 90 days exposure duration. Because of public health concern for children's exposures at NOA sites, studies where exposures begin as early in life as possible (e.g. 3 weeks of age) will be considered. Other exposure regimens will be considered, and include a low human relevant concentration with a 2 year exposure duration, and with a cumulative administered dose (concentration X time; CxT) in the same range as the CxT for the 90 day exposure groups.

Expected Outcome

There remains considerable uncertainty in the dose-response for adverse heath effects of asbestos and related mineral fibers, and by extension whether current environmental and occupational exposure standards are adequately protective of human health. There are likewise many gaps in current knowledge related to the physical and chemical determinants of mineral fiber toxicity and the mechanisms of fiber-induced adverse effects. A complete or even adequate understanding of the influence of fiber composition (durability and inherent bioreactivity) and morphology (durability and biodisposition) on toxic outcomes is beyond the scope of any one set of studies and will only be gained through long term and continued investment in fiber research. This NTP research program is designed to address some key outstanding issues regarding hazards of natural mineral fibers and contribute to advancing the field of fiber toxicology.

Regulatory efforts are in progress to revise health risk guidance values to account for mineral fiber type and size. The result of the proposed toxicology and carcinogenesis studies will be published as peer-reviewed NTP Technical Reports and data from the NTP studies can be directly used in risk assessment. A few examples of direct public heath impact follow. The U.S. EPA through its IRIS program is reassessing asbestos risk and intends to develop new RfC and carcinogenic unit risk values for asbestos fibers. These risk values are used by other EPA Offices and Regions when conducting site-specific risk assessments and determining the need for cleanup actions. The ATSDR develops Minimal Risk Values (MRLs) for hazardous substances which are used when providing guidance to communities as part of ATSDR public health consultations. The NIOSH Asbestos and Other Mineral Fibers Roadmap identifies a number of research areas that will "serve as the basis for evidence-based public health policies for asbestos and other mineral fibers" (NIOSH, 2007). Several of the research areas described in the Roadmap will be addressed by the proposed NTP research program. Lastly, there are many types of natural mineral fibers and synthetic fibers, including those generated through nanotechnology, for which adequate toxicological data do not exist. A better understanding of the determinants of fiber toxicity developed through this research program will instill greater confidence in the use of short-term toxicological methods for assessing the hazards of these fibers.

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